original article

Monitoring the effect of TNF-alpha inhibitors on laboratory parameters and adverse effects in different diseases: a retrospective, single-center study

Abdulaziz N. Madani,[a] Fahad M. Al-Saif,[a] Lama R. Alzamil,[a] Aljohara M. Almazroua,[b] Nuha A. Alfurayh,[a] Sara D. Aldokhayel,[a] Qais A. Almuhaideb,[b] Nouf S. Alballa,[a] Nujud A. Daham,[c] Abdulrahman A. Alkharashi[d]

From the [a]Department of Dermatology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [b]College of Medicine, King Saud University, Riyadh, Saudi Arabia; [c]Department of Dermatology, Derma Cinics, Riyadh, Saudi Arabia; [d]Department of Pharmacology, King Saud University, Riyadh, Saudi Arabia

Correspondence: Dr. Abdulaziz N. Madani · Department of Dermatology, College of Medicine, King Saud University, Riyadh 11417, Saudi Arabia · Amadani1@ksu.edu.sa · ORCID: https://orcid.org/0000-0001-7663-5115

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BACKGROUND: The introduction of biological treatments has revolutionized the management of moderate-to-severe psoriasis. Multiple clinical trials have established the efficacy of biological agents in the treatment of moderate-to-severe psoriasis. Nevertheless, there are no clear indications for optimal monitoring intervals during treatment.

OBJECTIVES: Collect and analyze laboratory evaluation data from patients receiving biological therapy to provide a better understanding of the need for laboratory investigations before and during treatment with biological agents, and to analyze adverse events and other factors.

DESIGN: Retrospective cohort

SETTINGS: Tertiary care center in Riyadh, Saudi Arabia.

PATIENTS AND METHODS: Data were collected from the electronic medical records of patients attending the dermatology, rheumatology, and gastroenterology clinics from June 2014 to June 2019. The laboratory parameters of patients who have received one of the TNF-alpha inhibitors (adalimumab, etanercept, or infliximab) were collected starting at baseline and up to at least one year from treatment initiation.

MAIN OUTCOME MEASURES: The time points at which patients developed significantly abnormal laboratory results during treatment with one of the TNF-alpha inhibitors.

SAMPLE SIZE: 250 patients

RESULTS: Most patients were treated with adalimumab (38.4%); a similar proportion (38%) with infliximab, whereas only 23.6% were treated with etanercept. The majority of the significant abnormal laboratory results occurred at baseline, 3-6 and 9-12 months. Most abnormalities were among patients using infliximab, followed by etanercept, and then adalimumab. The median number of laboratory abnormalities for dermatology patients was significantly lower than that for gastroenterology patients ($P<.001$), and for rheumatology patients ($P=.002$).

CONCLUSIONS: Because dermatology patients showed a lower median number of laboratory abnormalities than patients treated by other specialties in our study, we believe that dermatology patients require less frequent laboratory monitoring. Therefore, we

recommend laboratory evaluation at baseline, after 3–6 months, 1 year from the beginning of treatment, and annually thereafter for patients using TNF-alpha inhibitor agents. However, more frequent testing might be warranted according to patient comorbidities, concomitant medications, and physician judgment.

LIMITATIONS: Single center and retrospective design.

CONFLICT OF INTEREST: None.

Psoriasis is a chronic, immune-mediated inflammatory skin disorder affecting 1%–3% of the general population.[1,2] Although the exact etiology of psoriasis remains unclear, current evidence indicates that tumor necrosis factor-alpha (TNF-alpha) is a key mediator in the pathogenesis of psoriasis. Individuals with active skin disease have elevated levels of TNF-alpha in both blood and the lesional skin.[2] The TNF-alpha inhibitors infliximab, adalimumab, and etanercept, the biological agents approved for the treatment of moderate-to-severe plaque psoriasis,[3] have revolutionized the management of the disease. These agents target specific components of the immune system, thus possessing the advantages of being less immunosuppressive and generally safer than traditional systemic treatments.[4,5] Moreover, multiple clinical trials have established the efficacy of biological agents in the treatment of moderate-to-severe psoriasis. Nevertheless, there are no clear indications for optimal monitoring intervals during treatment.[6] Laboratory panels ordered for monitoring biological treatments vary between guidelines and in daily practice between physicians. Moreover, the frequency of testing differs considerably. For instance, The German guidelines recommend that a routine analysis be performed at the beginning of the study and at 1 and 3 months, followed by every 2-3 months for adalimumab. Similarly, routine analysis for etanercept is recommended at baseline and 1, 3, 6, and 8 months. For infliximab, the routine analysis is recommended at baseline, every month up to the 4th month, and every 2 months thereafter.[7] The European S3 Guidelines on the systemic treatment of psoriasis vulgaris recommend performing laboratory tests before treatment, at 4 and 12 weeks, and every 3 months thereafter for patients receiving adalimumab or etanercept.[8]

This study was conducted to collect and analyze laboratory evaluation data from patients receiving biological therapy to provide a better understanding of the need for laboratory investigations before and during treatment with biological agents and to analyze several other related factors.

PATIENTS AND METHODS

This investigation was retrospective cohort study. Data were extracted from the electronic medical records of all patients attending various clinics at King Saud University Medical City (KSUMC), a tertiary care center in Riyadh, Saudi Arabia. The study protocol was approved by the institutional review board. Because the data were obtained from medical records and anonymized, the requirement of obtaining informed consent was waived. For the purpose of this study, we retrospectively reviewed patient records from June 2014 to June 2019 to collect laboratory parameters starting at baseline—before the introduction of biological treatments—up to a minimum of one year from treatment initiation. Patients received one of the TNF-alpha inhibitor agents (adalimumab, etanercept, or infliximab), and were regularly followed up in the dermatology, rheumatology, or gastroenterology clinics of KSUMC, which are the most common specialties that use these medications.

Data abstraction from medical records concentrated on two major groups of data. The first group included demographic data, treatment characteristics, and previous treatments. The second group consisted of laboratory investigation results obtained at baseline and at each follow-up visit thereafter. These visits were generally scheduled at 3-month intervals, from baseline until 24 months after the initiation of treatment. Laboratory tests performed at each time point included the complete blood count (CBC) with differential counts, liver function tests (LFTs), total cholesterol level, low-density lipoprotein (LDL) level, triglyceride (TG) level, and renal function. Moreover, tuberculosis (TB) screening via interferon-gamma release assay, as well as hepatitis B virus (HBV), and hepatitis C virus (HCV) tests, were performed annually. Antinuclear antibody (ANA) and pregnancy tests were occasionally conducted in some patients.

Data were analyzed using the IBM SPSS Statistics V21.0 statistical software. A *P* value of <.05 was considered to be statistically significant. The assumption of normality for metric variables was evaluated using

a histogram and the Kolmogorov–Smirnov normality test. Levene's homogeneity test was used to evaluate the assumption of equal variances. The chi-square test of independence (χ^2 test) was used to evaluate the association between the time of the visit and the likelihood of having an abnormal laboratory result for all laboratory parameters. Furthermore, adjusted residuals were analyzed to further identify statistically significant time periods when abnormal laboratory results were observed. Follow-up visits were grouped into five time periods after the initial "baseline" visit, including 4 weeks and 3-6, 9-12, 15-18, and 21-24 months. Abnormal laboratory results were reported as "above" or "below" normal limits. The one-way ANOVA test was used to compare the frequency of abnormal laboratory results among patients managed by different medical teams.

RESULTS

We retrospectively reviewed the medical records of 250 patients. All patients received one of the TNF-alpha inhibitors as treatment for various autoimmune diseases. Most patients (58.8%) were women, and 43.2% were men aged between 12 and 79 years, with a median (IQR) age of 33.5 (24-48) years (**Table 1**). Almost half (49.6%) were aged between 21 and 40 years. Patients were cared for by three primary medical services, including 37.2% by dermatology, 34% by gastroenterology, and 28.8% by rheumatology services. Patients were treated with TNF-alpha inhibitors for various diseases such as psoriasis (32.8%), including 90.9% with chronic plaque psoriasis (CPS), 23.4% with psoriatic arthritis, and 9.1% with nail or guttate psoriasis. The latter two were either isolated or associated with CPS. Other conditions included Crohn's disease (29.2%), ulcerative colitis (4.8%), rheumatoid arthritis (21.2%), hidradenitis suppurativa (6%), and ankylosing spondylitis (3.6%). Of the 250 patients, 38% had associated comorbidities, with the majority being endocrine and metabolic diseases (17.2%) such as diabetes mellitus and dyslipidemia. The second most common comorbidities were cardiovascular diseases (14.8%) such as hypertension and coronary artery disease. Less frequent comorbidities are listed in **Table 1**.

Most patients were using adalimumab (38.4%), and a similar proportion (38%) were taking infliximab, whereas only 23.6% were using etanercept. The median duration of treatment was 20.0 months (25th to 75th percentiles: 10.0-32.0)

Half were concomitantly treated with other systemic agents, including immunosuppressive medications,

Table 1. Demographic and clinical characteristics of patients (n=250).

	n (%)
Gender	
Female	142 (56.8)
Male	108 (43.2)
Age groups (years)	
≤20	35 (14.0)
21-30	72 (28.8)
31-40	52 (20.8)
41-50	39 (15.6)
>50	52 (20.8)
Medical team	
Dermatology	93 (37.2)
Gastroenterology	85 (34.0)
Rheumatology	72 (28.8)
Principal diagnosis	
Psoriasis	82 (32.8)
Crohn's disease	73 (29.2)
Rheumatoid arthritis	53 (21.2)
Hidradenitis suppurativa	15 (6.0)
Ulcerative colitis	12 (4.8)
Ankylosing spondylitis	9 (3.6)
Other (i.e. Bechet's disease, sacroiliitis, sarcoidosis)	10 (4.0)
Psoriasis subtypes	
Plaque psoriasis	70 (90.9)
Psoriatic arthritis	18 (23.4)
Other: nail and guttate psoriasis	7 (9.1)
With comorbidity	95 (38.0)
Type of comorbidity	
Endocrine disease	43 (17.2)
Cardiovascular disease	37 (14.8)
Musculoskeletal disease	20 (8.0)
Respiratory disease	16 (6.4)
Hematologic/autoimmune disease	13 (5.2)
Gastrointestinal disease	11 (4.4)
Infectious disease	11 (4.4)
Central nervous system disease	9 (3.6)
Psychiatric illness	6 (2.4)
Renal disease	4 (1.6)

Data are n (%).

Table 2. Treatment characteristics (n=250).

The type of TNF-alpha inhibitor agent used	
Adalimumab	96 (38.4)
Infliximab	95 (38.0)
Etanercept	59 (23.6)
Median reatment duration (months)	20.0 (10.0-32.0)
Treatment continuation status	
Continued	218 (87.2)
Not continued	32 (12.8)
Duration of discontinued treatment (months)	23.1 (13.1)
Reasons for discontinuing the biological treatment	
Low drug efficiency	24 (9.6)
Pregnancy/planning for pregnancy	8 (3.2)
Drug reactions or other adverse effects	5 (2.0)
Other patient-related reasons: travel, intolerance	3 (1.2)
Infection	1 (0.4)
Concomitant use of other systemic treatments	125 (50.0)
Types of concomitant used systemic treatments (n=134)	
Azathioprine	56 (44.8)
Methotrexate	30 (24.0)
Antipsychotics/anticonvulsants	15 (12.0)
Prednisolone	13 (10.4)
Hydroxychloroquine	11 (8.8)
Sulfasalazine	9 (7.2)
Anti-TB medications	6 (4.8)
Leflunomide	3 (2.4)
Mesalazine	3 (2.4)
Antibiotics	2 (1.6)
Rituximab	1 (0.8)

Data are n (%) and median (25th to 75th percentiles) for treatment duration for those who discontinued treatment.

at the time of review. A small proportion of patients (12.8%) had their biological medications discontinued. The reasons reported for the discontinuation of treatment included 9.6% due to low drug efficiency, 3.2% due to pregnancy or planning to become pregnant, 2% due to drug reactions or other adverse effects, and 1.2% due to personal reasons related to patients. A few patients (0.4%) discontinued their TNF inhibitors due to infections (**Table 2**). A mild infection was defined as an infection that does not require any treatment (e.g., URTI). A moderate infection was treated in an outpatient setting with topical or systemic treatment, whereas a severe infection required hospital admission.[9] A minority of patients (n= 27) experienced complications during the follow-up period (**Table 3**).

Of 171 patients tested for TB infection at baseline using the QuantiFERON-TB test, a positive result was reported in 14 (5.6%) of patients (**Table 4**). At the 6-month follow-up, 50 patients were tested, of whom 1.6% were positive. Of the 24 patients tested at 12 months of follow-up, 1.2% showed a positive result. Only six patients were tested after the first year, and none were positive. Two-thirds of the patients were tested for HBV at the beginning of the study, and only one patient (0.4%) was positive. During the first year of follow-up, 15.6% of patients were tested for HBV, and

Table 3. Reported complications throughout the follow-up period (n=27).

Mild infection/inflammation	4 (14.8)
Moderate infection/inflammation	13 (48.1)
Severe infection/inflammation	4 (14.8)
Weight gain/loss attributed to drug	4 (14.8)
Reactivation of TB	1 (3.7)
Cardiovascular disease	1 (3.7)
Autoimmune disease	1 (3.7)
Neoplasm, benign, malignant, and not specified	1 (3.7)
Neurological disorders (multiple sclerosis-like symptoms, neuropathy)	1 (3.7)
Various other disorders, not requiring drug discontinuation (injection site reaction, gastrointestinal disorders, myalgia, fatigue, headache, mood change, pruritus)	5 (18.5)

Data are n (%).

only the patient who showed a positive result at the beginning of the study continued to be positive. During the second year of follow-up, none of the 5.6% of patients tested for HBV showed a positive result. Similarly, 60.4% of patients were tested for HCV at baseline, and only one patient showed a positive result. However, none of the 17.2% and 6% of patients who were tested during the second and third years, respectively, was positive. Occasional ANA testing was performed for some patients, which yielded variable results. A small proportion of women (4.2%) were tested for pregnancy at baseline and throughout the follow-up period, but none were positive.

The majority of the significantly abnormal laboratory results were found at baseline and 3-6 and 9-12 months (**Table 5**). Analysis of the LFT parameters revealed that the alanine aminotransferase test showed significantly more frequent abnormal results at 3-6 months than at other time points, whereas the most significant abnormalities in aspartate aminotransferase levels were observed at 9-12 months. Alkaline phosphatase, gamma-glutamyl transferase, and creatinine levels were significantly more abnormal at baseline. Significant abnormalities in total bilirubin levels were more frequent at 3-6 months than at baseline, whereas significant abnormalities in direct bilirubin levels were more frequent at 3-6 and 9-12 months.

Analysis of serum lipids revealed that all parameters, including total cholesterol, TG, and LDL, showed more significant abnormalities at baseline and 3-6 months than at other time points. Similarly, CBC analysis revealed that the serum white blood cell count, platelet count, and hemoglobin (Hb) level were more frequently significantly abnormal at baseline and 3-6 months from the start of TNF-alpha inhibitor treatment. Significant abnormalities in urinalysis were more frequent at baseline and 3-6 and 9-12 months. Overall, analysis of the association between each anti-TNF-alpha agent and the mean number of abnormal laboratory results revealed that most abnormalities were among patients using infliximab, followed by etanercept, and finally, adalimumab.

The results of one-way ANOVA showed that the mean number of abnormal laboratory findings differed significantly among patients managed by different medical teams [$F(2,247) = 11.41$, $P<.001$] (**Table 6**). Two pairs of Games-Howell adjusted post hoc comparison tests showed that the median number of laboratory abnormalities for dermatology patients was significantly lower than that for gastroenterology patients ($P<.001$), and for rheumatology patients ($P=.002$) (**Figure 1**). In contrast, the number of missing laboratory data was higher among rheumatology patients, followed by dermatology and gastroenterology patients. The pattern of decline in the mean number of abnormal laboratory results among the three medical services is presented in **Figure 1**.

An underlying kidney disease of any degree was associated with a statistically significantly higher rate of laboratory abnormalities over time on average. Patients with an underlying kidney disease were 32.1% ($P=.014$) times more likely to have abnormal laboratory results than patients without an underlying kidney disease, by accounting for the other predictors included in the analysis model. In contrast, patients with cardiovascular comorbidity showed a statistically nonsignificant increase in the rate of abnormal laboratory results over

Table 4. Laboratory data of tuberculosis, infectious and autoimmune serology and pregnancy tests (n=171).

	Not done	Normal	Abnormal
QuantiFERON test			
Baseline	79 (31.6)	157 (62.8)	14 (5.6)
At six months	200 (80)	46 (18.4)	4 (1.6)
At 12 months	226 (90.4)	21 (8.4)	3 (1.2)
At 18 months	245 (98)	5 (2)	0
At 24 months	249 (99.6)	1 (0.4)	0
Hepatitis B titer test			
Baseline	97 (38.8)	152 (60.8)	1 (0.4)
2nd year	211 (84.4)	38 (15.2)	1 (0.4)
3rd year	236 (94.4)	14 (5.6)	0
Hepatitis C titer test			
Baseline	99 (39.6)	150 (60)	1 (0.4)
2nd year	207 (82.8)	43 (17.2)	0
3rd year	235 (94)	15 (6)	0
Antinuclear antibody titer			
Baseline	186 (74.4)	28 (11.2)	36 (14.4)
2nd year	232 (92.8)	10 (4)	8 (3.2)
3rd year	247 (98.8)	1 (0.4)	2 (0.8)
Pregnancy test for females			
Baseline	136 (95.8)	6 (4.2)	0
2nd year	137(96.6)	5 (3.4)	0
3rd year	141 (99.3)	1 (0.7)	0

Data are n (%).

Table 5. Laboratory data for routine clinical chemistry and hematology tests.

	Baseline		4 weeks		3-6 months	
	Not done	Abnormal	Not done	Abnormal	Not done	Abnormal
Chemistry						
Alanine aminotransferase (u/L)	6 (2.4)	10 (4)	109 (43.6)	8 (3.2)	125 (25)	25 (5)[a]
Aspartate aminotransferase (u/L)	11 (4.4)	13 (5.2)	110 (44)	11 (4.4)	125 (25)	18 (3.6)
Alkaline phosphatase (u/L)	10 (4)	9 (3.6)[a]	110 (44)	7 (2.8)	124 (24.8)	13 (2.6)
Gamma-glutamyl transferase (u/L)	10 (4)	13 (5.2)[a]	111 (44.4)	6 (2.4)	139 (27.8)	11 (2.2)
Total bilirubin (umol/L)	4 (1.6)	8 (3.2)	110 (44)	7 (2.8)	126 (25.2)	28 (5.6)[a]
Direct bilirubin (umol/L)	10 (4)	30 (12)	113 (45.2)	15 (6)	138 (27.6)	68 (13.6)[a]
Creatinine (umol/L)	9 (3.6)	3 (1.2)[a]	115 (46)	1 (0.4)	134 (26.8)	1 (0.2)
Serum lipids						
Hypertriglyceridemia	137 (54.8)	16 (6.4)[a]	218 (87.2)	5 (2)	389 (77.8)	23 (4.6)[a]
Low density lipoprotein	140 (56)	110 (44)[a]	221 (88.4)	29 (11.6)	396 (79.2)	104 (20.8)[a]
Total cholesterol	137 (54.8)	113 (45.2)[a]	219 (87.6)	31 (12.4)	396 (76.2)	104 (20.8)[a]
Complete blood count and differential						
Hemoglobin	7 (2.8)	78 (31.2)[a]	109 (43.6)	43 (17.2)	125 (25)	94 (18.8)[a]
White blood cell count	6 (2.4)	36 (14.4)[a]	109 (43.6)	19 (7.6)	123 (24.6)	43 (8.6)
Neutrophils	34 (13.6)	36 (14.4)[a]	121 (48.4)	28 (11.2)	148 (29.6)	76 (15.2)[a]
Lymphocytes	33 (13.2)	60 (24)[a]	120 (48)	42 (16.8)	149 (29.8)	115 (23)[a]
Monocytes	33 (13.2)	77 (30.8)[a]	120 (48)	51 (20.4)	150 (30)	138 (27.6)[a]
Eosinophils	33 (13.2)	12 (4.8)	120 (48)	6 (2.4)	148 (29.6)	30 (6)[a]
Basophils	33 (13.2)	25 (10)[a]	120 (48)	12 (4.8)	148 (29.8)	30 (6)
Platelet count	8 (3.2)	20 (8)[a]	110 (44)	10 (4)	123 (24.6)	19 (3.8)
Urinalysis	124 (49.6)	126 (50.4)[a]	160 (64)	90 (36)	301 (60.2)	199 (39.8)[a]

Data are n (%). [a]Cells with standardized adjusted residual ≥1.96 or <1.96

time. The presence of other comorbidities showed no significant correlation with the rate of abnormal laboratory results.

DISCUSSION

The use of biological therapy worldwide is markedly increasing. TNF-alpha inhibitors are among the first biological medications used, specifically in dermatology.[10] To our knowledge, various recommendations have been provided on the appropriate laboratory tests for patients receiving biological medications; however, to date, few studies have been published on the appropriate screening intervals for patients receiving biological medications. This has resulted in a significant variability between physicians in different specialties and physicians in the same specialty when ordering laboratory tests. Ordering excessive unwarranted tests may be unnecessarily expensive. Such use of valuable medical resources is also a waste of physician time and

Table 5 (cont). Laboratory data for routine clinical chemistry and hematology tests.

	9-12 months		15-18 months		21-24 months		*P* value
	Not done	Abnormal	Not done	Abnormal	Not done	Abnormal	
Chemistry							
Alanine aminotransferase (u/L)	139 (27.8)	20 (4)[a]	287 (57.4)	7 (1.4)	330 (66)	8 (1.6)	**<.001**
Aspartate aminotransferase (u/L)	140 (28)	24 (4.8)[a]	58 (9)	12 (2.4)	331 (66.2)	6 (1.2)	**<.001**
Alkaline phosphatase (u/L)	137 (27.4)	9 (1.8)	290 (58)	8 (1.6)	332 (66.4)	1 (0.2)	**<.001**
Gamma-glutamyl transferase (u/L)	143 (28.6)	16 (3.2)	289 (57.8)	15 (3)	332 (66.4)	8 (1.6)	**<.001**
Total bilirubin (umol/L)	137 (27.4)	19 (3.8)	288 (57.6)	18 (3.6)	331 (66.2)	10 (2)	**<.001**
Direct bilirubin (umol/L)	141 (28.2)	60 (12)[a]	291 (58.2)	38 (7.6)	336 (67.2)	32 (6.4)	**<.001**
Creatinine (umol/L)	141 (28.2)	1 (0.2)	288 (57.6)	2 (0.4)	335 (67)	0	**<.001**
Serum lipids							
Hypertriglyceridemia	396 (79.2)	20 (4)	455 (91)	9 (1.8)	466 (93.2)	8 (1.6)	**<.001**
Low density lipoprotein	411 (82.2)	89 (17.8)	466 (93.2)	34 (6.8)	473 (94.6)	27 (5.4)	**<.001**
Total cholesterol	410 (82)	90 (18)	466 (93.2)	34 (6.8)	472 (94.4)	28 (5.6)	**<.001**
Complete blood count and differential							
Hemoglobin	132 (26.4)	76 (15.2)	291 (58.2)	44 (8.8)	333 (66.6)	29 (5.8)	**<.001**
White blood cell count	131 (26.2)	40 (8)	289 (57.8)	29 (5.8)	333 (66.6)	13 (2.6)	**<.001**
Neutrophils	159 (31.8)	72 (14.4)[a]	304 (60.8)	38 (7.6)	343 (68.6)	23 (4.6)	**<.001**
Lymphocytes	161 (32.2)	107 (21.4)[a]	304 (60.8)	65 (13)	343 (68.6)	117 (23.4)	**<.001**
Monocytes	160 (32)	132 (26.4)[a]	304 (60.8)	83 (16.6)	343 (68.6)	69 (13.8)	**<.001**
Eosinophils	161 (32.2)	23 (4.6)	304 (60.8)	8 (1.6)	343 (68.6)	12 (2.4)	**<.001**
Basophils	159 (31.8)	38 (7.6)[a]	304 (60.8)	12 (2.4)	343 (68.6)	13 (2.6)	**<.001**
Platelet count	132 (26.4)	16 (3.2)	290 (58)	9 (1.8)	333 (66.6)	6 (1.2)	**<.001**
Urinalysis	316 (63.2)	184 (36.8)[a]	375 (75)	125 (25)	396 (79.2)	104 (20.8)	**<.001**

Data are n (%). [a]Cells with standardized adjusted residual ≥1.96 or <1.96

negatively impacts patient compliance with treatment. However, not performing the necessary tests could delay the detection of certain complications. In this retrospective study, we shared our local experience in analyzing the data of patients receiving infliximab, adalimumab, or etanercept who were followed up in the dermatology, gastroenterology, or rheumatology clinics to highlight the time points at which these patients developed significantly abnormal laboratory results and to analyze other related factors.

The general consensus is that all patients should be carefully questioned and examined before initiating biological therapy. Obtaining a complete medical history is essential, including general health conditions, chronic diseases, existing medications, and detailed family and personal medical histories. Before initiating treatment with a TNF-alpha inhibitor, caution is advised in patients with a history or risk of developing congestive heart failure, demyelinating disorders, seizures, or malignancies. Although the Food and

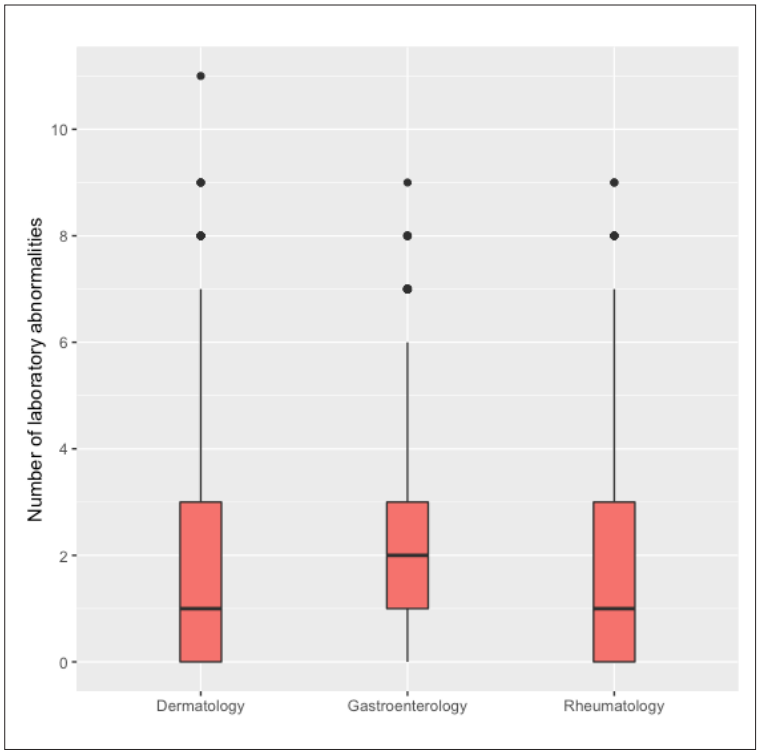

Figure 1. Number of laboratory abnormalities by medical specialty (median, interquartile range).

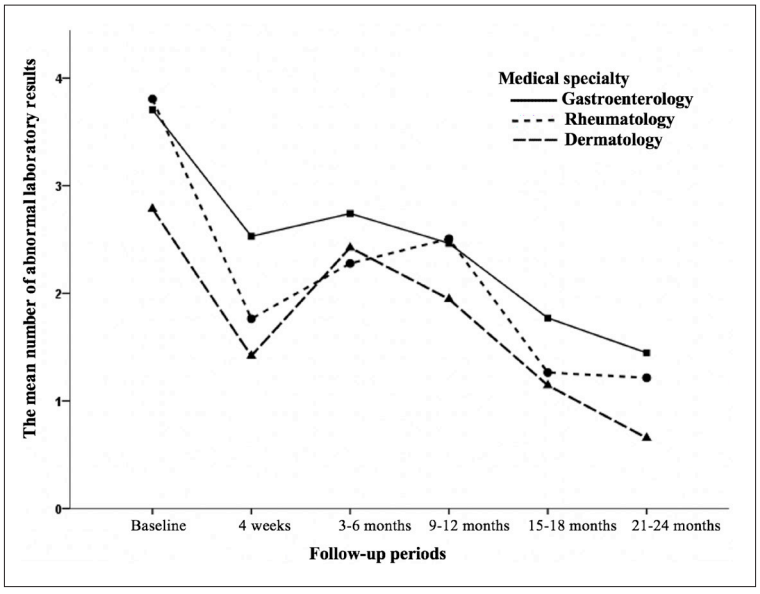

Figure 2. Subgroup analysis of the mean number of abnormal laboratory results among the three medical specialties.

Drug Administration recommends certain screening tests before the initiation of biological therapy, the majority of evidence is derived from single or multiple clinical trials exploring the overall safety and efficacy of the medication, rather than the appropriateness of screening.[11]

There is acceptable evidence from clinical trials and postmarketing surveillance that supports the absence of routine pretreatment screening with urinalysis, chest radiograph, and metabolic panels before starting treatment with any of the biological agents.[11] However, in our study, the most important abnormal laboratory results occurred at baseline and at the beginning of the treatment results, in addition to other time points within the first year of starting treatment, as shown in **Table 5**. A possible explanation is that the majority of these abnormal laboratory results were among patients using infliximab, which is primarily used by gastroenterology specialists to treat patients with inflammatory bowel disease. The underlying inflammatory state, the debilitating nature of the disease, and the previous or concomitant use of immunosuppressive medications in those patients are all possible factors that contribute to these findings. Our primary objective in conducting laboratory investigations before initiating biological therapy is to detect preexisting abnormalities that could present a contraindication to initiating biological therapy or act as risk factors for future complications. We also aim to provide baseline values for future reference.

Routine baseline CBC, LFT, and renal profile are recognized to be performed before the initiation of biological therapy and are repeated every 3–6 months.[12] Conversely, a prospective cohort study over 5 years was conducted on 162 patients with psoriasis, which had investigated the frequency of serious abnormal laboratory parameters during etanercept or adalimumab treatment. It had concluded that the incidence of biologic therapy-related serious laboratory abnormalities was low;[12] hence, their findings do not support the need for routine laboratory testing beyond the laboratory tests required to monitor concomitant systemic treatments and/or comorbidities.

In our study, **Figure 2** showed that the mean number of abnormal laboratory results decreased between baseline and 4 weeks after treatment; slightly decreased at 4 weeks (P=.061), increased significantly between 3 and 6 months by a factor equal to 6.1% (P<.001), slightly decreased at 9–12 months, and then decreased steadily after 12 months.

The practice in Saudi Arabia in monitoring patients using biologics is highly variable among physicians.[13]

Table 6. Bivariate analysis of the treatment and laboratory characteristics among the three medical specialties.

	Dermatology (n=93)	Gastroenterology (n=85)	Rheumatology (n=72)	Test statistic (df1, df2)	*P* value
TNF-alpha inhibitor					
Etanercept	14 (15.1)	0	45 (62.5)	$\chi^2(4)=252.41$	**<.001**
Adalimumab	76 (81.7)	5 (5.9)	15 (20.8)		
Infliximab	3 (3.2)	80 (94.1)	12 (16.7)		
Concomitant use of other systemic treatments					
No	78 (83.9)	26 (30.6)	21 (29.2)	$\chi^2(2)=67.99$	**<.001**
Yes	15 (16.1)	59 (69.4)	51 (70.8)		
Reported complications throughout treatment					
No	88 (94.6)	74 (87.1)	61 (84.7)	$\chi^2(2)=4.74$	.093
Yes	5 (5.4)	11 (12.9)	11 (15.3)		
Missing laboratory tests	23.1 (9.1)	19.2 (6.8)	24.00 (8.1)	F(2,247)=15.73	**<.001**
Abnormal laboratory results	1.7 (2.0)	2.3 (1.8)	2.0 (2.1)	F(2,247)=11.41	**<.001**

Data are n (%) and mean (standard deviation) for missing laboratory tests and abnormal laboratory results. df1: Between Groups degrees of freedom, df2: Within Groups [Error] degrees of freedom for ANOVA.

Screening for TB is recommended for all patients before taking a TNF-alpha inhibitor, especially in endemic areas.[14] According to the Saudi guidelines for the testing and treatment of latent TB infection, screening for an active or latent TB infection is mandatory before initiating treatment with any biological agent, as the risk of reactivation of TB has been associated with the use of biological therapy.[14] Moreover, patients on TNF-alpha inhibitor treatments are at increased risk of developing TB compared with patients receiving conventional systemic antipsoriatic treatments.[15] Several cases of TB reactivation have been reported in patients receiving TNF-alpha inhibitor therapy.[16] Therefore, we recommend that all patients undergoing biological therapy be tested for TB infection before initiating treatment and annually throughout the treatment duration. Furthermore, a meta-analysis of withdrawal rates and adverse events conducted by Schmitt et al, evaluating the tolerability of biological treatments in patients with moderate-to-severe psoriasis, showed that the monthly rates of withdrawals due to adverse events were 1.3% for infliximab, which frequently causes infusion reactions, and below 1% for etanercept and adalimumab, which are associated with injection site reactions and upper respiratory tract infections, respectively.[17] As shown in **Table 3**, most of our study patients did not experience any side effects during the treatment follow-up period. A small proportion of patients developed moderate (5.2%) or severe (1.6%) infections. Previous studies have revealed that concern for increased infection risk is most significant with long-term use of infliximab.[18,19] In a retrospective cohort study by Kimball et al, the incidence rate of hospitalized infectious events was higher for infliximab than for other treatment groups, including adalimumab and etanercept, with the latter having the lowest rate of infectious events.[20]

Only one patient experienced a cardiovascular event in our study, as shown in **Table 3**. Rungapiromnan et al conducted a systematic review and meta-analysis to assess the impact of biologics (adalimumab, etanercept, and infliximab) on the risk of major adverse cardiovascular events in patients with psoriasis. The researchers concluded that there were no statistically significant differences in the risk of major adverse cardiovascular events associated with these biologics.[21]

Table 1 shows that 38% of our patients had comorbidities, and most of them were endocrine (17.2%) and cardiovascular (14.8%) diseases. We found that patients with cardiovascular comorbidities who are using biologics had a slight but not statistically significant increase in the rate of abnormal laboratory results during their follow-up period. Other comorbidities showed no significant correlation with

the rate of abnormal laboratory results.

In conclusion, because of their safety and effectiveness, biologics are considered a fundamental therapeutic modality for various dermatological diseases, including moderate-to-severe CPS. Because dermatology patients showed a lower mean number of laboratory abnormalities than patients treated by other specialties in our study, we believe that dermatology patients require less frequent laboratory monitoring. The majority of significant abnormal laboratory results were found at baseline and at 3-6 and 9-12 months. Therefore, we recommend laboratory evaluation at baseline, after 3-6 months, at 1 year from the beginning of treatment, and annually thereafter for patients using TNF-alpha inhibitors. However, more frequent testing might be warranted according to patient comorbidities, concomitant medications, and the physician's judgment. Further research with a larger sample size is recommended to confirm our study findings.

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